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(54) Title: COSMETIC COMPOSITION CONTAINING ALPHA HYDROXY ACIDS

(57) Abstract

A skin treatment composition is provided comprising a skin benefit ingredient selected from the group consisting of an alpha hydroxy acid, a salt or ester thereof, and mixtures thereof and a chelating agent. Suitable chelating agents have a high affinity with zinc and/or magnesium ions, more specifically the chelating agent is selected from the group consisting of chelating agents having an affinity with zinc ion of greater than 9.2, chelating agents having an affinity with magnesium ion of greater that 1.9, and mixtures thereof.

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COSMETIC COMPOSITION CONTAINING ALPHA-HYDROXY ACIDS

FIELD OF THE INVENTION:

The invention relates to skin treatment compositions containing an alpha hydroxy acid or an ester or a salt thereof in combination with specific chelating agents.

BACKGROUND TO THE INVENTION:

Alpha hydroxy acids are emerging as accepted ingredients for improving the appearance of dry, flaky, wrinkled, aged, photodamaged skin and for treating various disorders of skin, e.g., hyperkeratosis, ichthyosis, skin blemishes, acne, warts, herpes, psoriasis, eczema, pruritis. It is believed that alpha hydroxy acids act, at least in part, through stimulating the desquamation of outer corneocytes of stratum corneum. Unfortunately, the use of alpha hydroxy acids, particularly those containing eight or more carbon atoms, may be accompanied by an unpleasant sensory perception, e.g., stinging, and occasionally, an irritation of the skin. Therefore, it has been necessary to minimize the concentration of alpha hydroxy acids in skin treatment compositions, even though generally, the higher the concentration of the alpha hydroxy acid the better is the effect with regard to eliminating or preventing skin dryness, aging, or skin disorders.

Some chelating agents, such as EDTA (ethylene diamine tetraacetic acid), have been previously included in cosmetic compositions containing alpha hydroxy acids. However, EDTA was included in prior art compositions at minute concentrations (i.e., not greater than 0.1%) as a preservative. Prior art does not envision that the use of EDTA or other strong zinc and/or magnesium chelators in an

effective amount with an alpha hydroxy acid may result in substantial improvement of the acid's activity, i.e., prior art does not envision synergistic combinations of a specific class of chelating agents and alpha hydroxy acids taught by the present invention.

Accordingly, it is an object of the present invention to provide a skin treatment composition containing an alpha hydroxy acid, or derivatives thereof, in combination with an ingredient which enhances the activity of the acid.

It is another object of the invention to provide a method for treating or preventing the appearance of wrinkled, flaky, aged, photodamaged skin or skin disorders.

It is yet another object of the invention to attain the treatment of the skin with a composition containing an alpha hydroxy acid, or derivative thereof while avoiding or substantially minimizing the irritation of the skin and the perception of stinging.

These and other objects of the invention will become more apparent from the detailed description and examples which follow.

SUMMARY OF THE INVENTION:

The invention includes skin treatment compositions containing an alpha hydroxy acid, or their derivatives (salts or esters) (hereafter called collectively "alpha hydroxy acid") as a skin benefit ingredient. The product according to the invention further includes a chelating agent, selected from specific classes of chelating agents, as an activity enhancer for the alpha hydroxy acid. The chelating agent suitable for use in the present invention is selected from chelators which have high affinity with zinc and/or magnesium ions. The presence of the activity

enhancer in the inventive product substantially improves the performance of an alpha hydroxy acid, i.e., the activity enhancer substantially increases the ability of an alpha hydroxy acid to release corneocytes from stratum corneum. The activity enhancer has no or little effect on improving skin benefit when used alone; it is only when combined wiith an alpha hydroxy acid that a substantial increase in skin benefit is realized. In short, the present invention is based, at least in part, on the discovery of synergistic interaction between alpha hydroxy acids and certain chelating agents.

In a preferred embodiment of the invention, the chelating agent is used in conjunction with longer chain alpha hydroxy acids (e.g., those containing at least 8 carbon atoms and, preferably, 10 or more carbon atoms) in order to attain an even more beneficial synergistic combination.

According to the present invention, by virtue of including an effective amount of a specific chelating agent into alpha hydroxy acid containing compositions, the performance of the compositions is substantially improved. Alternatively, lower levels of an alpha hydroxy acid may be included in the composition containing the chelating agent to equal the performance of a similar formulation without the chelating agent, in order to minimize adverse reactions, such as skin irritation and stinging sensation.

The present invention also includes a method of improving or preventing the appearance of wrinkled, flaky, aged, photodamaged skin and treating skin disorders, which method includes applying to the skin a composition containing an alpha hydroxy acid and an activity enhancing amount of a chelating agent which has high affinity with zinc and/or magnesium ions.

Compositions of the invention are intended for topical

application to mammalian skin which is already in dry, flaky, wrinkled, aged, photodamaged condition or which suffers from a skin disorder, or, in the alternative, the inventive compositions may be applied prophylactically to normal healthy skin to prevent or reduce the deteriorative changes.

The inventive compositions contain, as a first essential ingredient, a skin benefit agent selected from the group consisting of an alpha hydroxy acid, a salt of an alpha hydroxy acid, an ester of an alpha hydroxy acid, and mixtures thereof. All the above listed suitable skin benefit ingredients are collectively termed herein "alpha hydroxy acid."

The alpha hydroxy acid or its ester has the following structure:

$$R_2CHOHCOOR_1$$

wherein R_1 and R_2 are H, alkyl, aralkyl or aryl group of saturated or unsaturated, isomeric or non-isomeric, straight or branched chain or cyclic form, having 1 to 30 carbon atoms, and in addition R_2 may carry F, Cl, Br, I, N, S, OH, CHO, COOH and alkoxy group having 1 to 9 carbon atoms. The alpha hydroxy acids may be present as a free acid or an ester form, or in a salt form with an organic base or an inorganic alkali. The typical alkyl, aralkyl and aryl groups for R_1 and R_2 include methyl, ethyl, propyl, isopropyl, butyl, pentyl, octyl, lauryl, stearyl, benzyl and phenyl, etc.,

D, DL, or L stereoisomeric forms of an alpha hydroxy acid may be employed in the inventive compositions.

Examples of suitable alphahydroxy acids include but are not limited to:

alpha hydroxy acetic acid (also known as "glycolic acid")
alpha hydroxypropionic acid (also known as "lactic acid")
alpha hydroxytetranoic acid
alpha hydroxyhexanoic acid
alpha hydroxyoctanoic acid (also known as "alpha hydroxy caprylic acid")
alpha hydroxynonanoic acid
alpha hydroxydecanoic acid
alpha hydroxyundecanoic acid
alpha hydroxydodecanoic acid (also known as "alpha hydroxy lauric acid")
alpha hydroxytetradecanoic acid
alpha hydroxyhexadecanoic acid

alpha hydroxyoctadecanoic acid
alpha hydroxyoctaeicosanoic acid,

and mixtures thereof.

Examples of suitable esters of alpha hydroxy acids include but are not limited to:

alpha hydroxypropionic acid ethyl ester
alpha hydroxypropionic acid propyl ester
alpha hydroxytetranoic acid ethyl ester
alpha hydroxyhexanoic acid methyl ester
alpha hydroxyhexanoic acid ethyl ester
alpha hydroxyoctanoic acid hexyl ester
alpha hydroxyoctanoic acid methyl ester
alpha hydroxyoctanoic acid ethyl ester
alpha hydroxyoctanoic acid pentyl ester
alpha hydroxyoctanoic acid octyl ester
alpha hydroxyoctadecanoic acid ethyl ester
alpha hydroxyoctanoic acid monoglyceride
alpha hydroxyoctanoic acid diglyceride
alpha hydroxyoctanoic acid triglyceride, and mixtures thereof.

Suitable salts of alpha hydroxy acids include but are not limited to sodium, potassium, ammonium, triethanolamine, calcium, lithium salts. The salts may be obtained commercially or they may be prepared by methods known in the art, e.g., neutralizing an alpha hydroxy acid with a suitable base, such as hydroxide bases of ammonium, potassium, sodium.

Preferably, to attain maximum performance, a mixture of alpha hydroxy acids is employed in the compositions according to the invention. The optimum performance is attained when a mixture of lactic acid, alpha hydroxy octanoic acid and alpha hydroxy lauric acid is employed.

It has been found, as part of the present invention, that an L-form of alpha hydroxy acids is superior to the D-form of alpha hydroxy acid. Accordingly, in order to maximize performance at reduced levels of alpha hydroxy acids, in the most preferred embodiment of the invention, inventive compositions contain the L-form of an alpha hydroxy acid. Preferred compositions according to the invention contain at least 60% of an alpha hydroxy acid in L-configuration, by weight of total alpha hydroxy acid.

Preferably, in order to attain optimum performance, the inventive compositions contain from 60% to more than 99%, most preferably more than 99% of alpha hydroxy acids by weight of total hydroxy acids in the composition is in the L-form.

The total amount of alpha hydroxy acid in the inventive compositions ranges from 0.001% to 70%, preferably from 0.1% to 20%, and most preferably from 1% to 10% by weight of the composition, in order to attain maximum performance at optimal cost.

Preferably, in order to attain a substantial benefit from

the presence of the activity enhancer, the total concentration of alpha hydroxy acids in the inventive compositions is at least 0.1% by weight of the composition.

The second essential ingredient of inventive compositions is a chelating agent. Chelating agents included in inventive compositions have a high affinity with zinc and/or magnesium ions.

Specifically, the chelating agent suitable for inclusion in inventive compositions is selected from the group consisting of chelating agents having an affinity with zinc ion of greater than 9.2, chelating agents having an affinity with magnesium ion of greater than 1.9, and mixtures thereof.

The affinity of a chelating agent for magnesium and/or zinc ions may be calculated as follows:

A chelator is characterized by the pK values and the absolute stability constant of its complex with a given metal ion. This allows the apparent stability constants to be calculated. The chelate formation constant or stability constant is a measure of the stability of the various chelator-metal complexes and quantifies the affinity of the metal for the chelator.

Log K values are contained in Critical Stability Constants, Volume 1: Amino Acids, Arthur E. Martell and Robert M. Smith (1974), Plenum Press, New York. The values for Log K were typically at 25°C and 0.1M ionic strength. Log K values were normalized (adjusted for pH 7.4) to permit comparison of chelators by using the following formula obtained from Fluka BioChemika, "Basics for Biochemistry 'MicroSelect'" page 31 (1988), which may be obtained from Fluka Chemical Corporation, 980 South Second Street, Ronkonkoma, New York 11779.

Thus, normalized value = Log $K_{1\,(apparent,\ pH\ x)}$ = Log K - Log α where x = 7.4 and $\alpha = [H^+]^n (K_n K_{n-1} \ldots K_2 . K_1)^{-1} + [H^+]^{n-1} (K_n . K_{n1} \ldots K_2)^{-1} + \ldots + [H^+]^2 (K_n . K_{n-1})^{-1} + [H^+]^1 (K_n)^{-1} + 1$;

where n = deprotonable groups
with $PK_1 < PK_2 \ldots PK_n$ and $K_i = 10^{-pKi}$ at pH X,
with $[H^+] = 10^{-x}$.

Therefore, in order to determine whether a chelator is suitable for use in the inventive compositions log K_1 at pH 7.4 must be calculated for magnesium and zinc ions. If log K_1 for zinc ion is greater than 9.2 and/or log K_1 for magnesium ion is greater than 1.9, the chelator is suitable for use in inventive compositions.

Affinity of some chelating agents with magnesium and zinc ions are given in Table I. Log K values, except where indicated otherwise, were obtained from Critical Stability Constants, Volume 1: Amino Acids, Arthur E. Martell and Robert M. Smith (1974), Plenum Press, New York.

TABLE 1 **METAL ION AFFINITY (Log K_1)**

	Log K_1 (at pH 7.4)		Log K		
CHELATOR	Mg^{2+}	Zn^{2+}	H^+	Mg^{2+}	Zn^{2+}
EDTA (amino carboxylate)	6.0	13.6	10.17 (K_6) 6.11 (K_5) 2.68 (K_4) 2.0 (K_3)	8.79	16.44
EGTA (amino carboxylate)	1.9	9.2	9.40 (K_4) 8.78 (K_3) 2.66[a] (K_2) 2.0[a] (K_1)	5.28	12.6
Pyrophosphate (di-phosphoric acids)	2.8	6.1	8.37 (K_4) 9.0 (K_3)[f] 6.04 (K_2) 6.19 (K_1)[f]	5.42	8.7[b]
Tripolyphosphate (polyphosphate)	4.0	5.7	8.00 (K_4) 8.70 (K_3)[f] 5.50 (K_2) 5.90 (K_1)[f]	5.76	7.5

CHELATOR	Log K_1 (at pH 7.4)		Log K		
	Mg^{2+}	Zn^{2+}	H^+	Mg^{2+}	Zn^{2+}
L-cysteine methyl ester (amino acid ester)	N.A.**	14.3	8.93 (K_2) 6.53 (K_1)	N.A.	15.91
DL-(Methylethylene)dinitrilo tetra acetic acid (PDTA) (tertiary amine)	N.A.	13.9	10.84 (K_4) 6.2 (K_3) 2.78 (K_2)[a] 1.87*K_1)[a]	N.A.	17.3
trans-Decahydronaphthylene-trans-2,3-bis iminodiacetic acid (teriary amine)	7.2	N.A.	10.61 (K_4) 6.47 (K_3) 3.04 (K_2) 2.26 (K_1)	10.36	N.A.
Aminophenyl menthylene diphophonic acid (aminophophonic acid)	3.6	7.8	10.29 (K_4) 8.17 (K_3) 5.29 (K_2) 1.6 (K_1)	7.39	11.64

	Log K_1 (at pH 7.4)		Log K		
CHELATOR	Mg^{2+}	Zn^{2+}	H^+	Mg^{2+}	Zn^{2+}
Ethylene-N,N'(2,6-dicarboxy) piperdine (imino diacetic acid derivative)	2.5	11.2	10.30 (K_4) 6.98 (K_3) 2.64 (K_2) 2.0 (K_1)	6.36	15.08
Adenosine triphosphate (Azine)	4.9	5.7	6.51 (K_2) 4.06 (K_1)	4.06	4.85
8-hydroxyquinoline	2.0	6.1	9.66 (K_2) 4.99 (K_1)	4.31[a]	8.52
Nitrilotriacetic Acid (NTA) (amino carboxylic acid)	3.2	8.4	9.65 (K_3) 2.48 (K_2) 1.8 (K_1)	5.47	10.66
Diethylenetrinitrilopenta-acetic Acid (DTPA)[e] (tertiary amine)	5.0	14.4	10.5 (K_5) 8.6 (K_4) 4.26 (K_3) 2.41 (K_2) 2.08 (K_1)	9.3	18.75

	Log K_1 (at pH 7.4)		Log K		
CHELATOR	Mg^{2+}	Zn^{2+}	H^+	Mg^{2+}	Zn^{2+}
N-(2-Hydroxyethyl) ethylenedinitrilo-N,N',N'triacetic acid (HEDTA)[c] (iminodiacetic acid derivative)	4.5	12.0	9.86 (K_3) 5.31 (K_2) 2.51 (K_1)	7.0	14.5

** not available

[a] measured at 20°C, 0.1M ionic strength

[b] measured at 25°C, 0.01M ionic strength

[c] Log K values obtained from CRC Handbook of Organic Analytical Reagents, Cheng et al., (CRC Press, Boca Raton, 1982)

[f] measured with $(CH_3)_4N$ used as a background electrolyte

A sample calculation for magnesium ion affinity with pyrophosphate at pH 7.4 is as follows:

$$\alpha = [H]^4/(K_4K_3K_2K_1) + [H]^3/(K_4K_3K_2) + [H^+]^2/K_4K_3 + [H^+]/K_4 +$$

$$1 = [10^{-7.4}]^4/(10^{-8.4})(10^{-9.0})(10^{-6.0})(10^{-6.2}) + [10^{-7.4}]^3/(10^{-8.4})(10^{-9.0})(10^{-6.0}) + [10^{-7.4}]^2/(10^{-8.4})(10^{-9.0}) + [10^{-7.4}]/(10^{-8.4}) +$$

$$1 = 10^{-29.6}/10^{-29.6} + 10^{-22.2}/10^{-23.4} + 10^{-14.8}/10^{-17.4} + 10^{-7.4}/10^{-8.4} +$$

$$1 = 10^0 + 10^{1.2} + 10^{2.6} + 10^1 + 1 = 1 + 15.8 + 398.1 + 10 + 1 = 425.9$$

$\alpha = 425.9$

$\text{Log } \alpha = 2.63$

$\text{Log } K_1 = \text{Log } K - \text{Log } \alpha$

$\text{Log } K_1 = 5.4 - 2.6 = 2.8$

All chelators listed in Table 1, except EGTA, are suitable for use in the inventive compositions.

Suitable chelating agents may be selected from (among others) aminocarboxylic acids or salts thereof, polyphosphoric acids or salts thereof, diphosphonic acids, salts of diphosphonic acids, tertiary amines, aminophosphonic acids, iminodiacetic acid derivatives, azines, hydroxyquinolines, and amino acid esters as long as the chelating agent has the affinity with zinc ion of greater than 9.2 and/or the affinity with magnesium ion of greater than 1.9.

Examples of suitable chelating agents include but are not limited to ethylene diamine tetraacetic acid, a salt of ethylene diamine tetraacetic acid, sodium pyrophosphate, sodium tripolyphosphate, 8-hydroxyquinoline, DL-(Methylene)dinitrolo tetra acetic acids, trans-decahydronaphthylene-trans-2, 3-bis-iminodiacetic, aminophenyl methylene diphosphonic acid, ethylene-bis-N,N1-(2,6-carboxyl) piperdine, adenosine triphosphate, L-cysteine methyl ester and 8-hydroxyquinoline.

The most preferred chelating agents according to the present invention are EDTA and/or pyrophosphate, and/or 8-hydroxy quinoline due to their ready availability, excellent performance, relatively low cost, and safety in use.

Of course, chelating agents, other than the ones listed above, may be employed in the inventive compositions as long as the chelating agent has the affinity with zinc ion of greater than 9.2 and/or the affinity with magnesium ion of greater than 1.9.

The chelating agent is employed in the inventive compositions in the amount effective to enhance the activity of an alpha hydroxy acid. The precise amount will depend on the particular chelating agent and alpha hydroxy acid included in the inventive compositions. Typically, the amount is greater than 0.1%, preferably at least 0.2% by weight of the composition, most preferably in the range of from 0.2% to 2% to attain maximum performance at optimal cost.

The skin treatment composition of the invention also includes a therapeutically acceptable vehicle or a carrier which is inert, usually an ingredient present in highest amounts, and functioning to deliver active or performance ingredients. The amount of vehicle may suitably range from 2 to 99%, preferably from 5 to 80%, most preferably from 25 to 80%, by weight of the total compositions.

Surfactants, which are also sometimes designated as emulsifiers, may be incorporated into the cosmetic compositions of the present invention. Surfactants can suitably comprise anywhere from 0.5 to 30%, preferably from 1 to 15% by weight of the total composition. Surfactants may be cationic, nonionic, anionic, or amphoteric in nature and combinations thereof may be employed.

Illustrative of the nonionic surfactants are alkoxylated compounds based upon fatty alcohols, fatty acids and sorbitan. These materials are available, for instance, from the Shell Chemical Company under the "Neodol" designation. Copolymers of polyoxypropylene-polyoxyethylene, available under the Pluronic trademark sold by the BASF Corporation, are sometimes also useful. Alkyl polyglycosides available from the Henkel Corporation similarly can be utilized for the purposes of this invention.

Anionic-type surfactants may include fatty acid soaps (polyglyceryl oleates), sodium lauryl sulphate, sodium lauryl ether sulphate, alkyl benzene sulphonate, mono and dialkyl acid phosphates and sodium fatty acyl isethionate.

Amphoteric surfactants include such materials as dialkylamine oxide and various types of betaines (such as cocoamido propyl betaine).

Emollients are often incorporated into cosmetic compositions of the present invention. Levels of such emollients may suitably range from 0.5 to 50%, preferably between 5 and 30% by weight of the total composition. Emollients may be classified under such general chemical categories as esters, fatty acids and alcohols, polyols and hydrocarbons.

Esters may be mono- or di-esters. Acceptable examples of fatty di-esters include dibutyl adipate, diethyl sebacate, diisopropyl dimerate, and dioctyl succinate. Acceptable branched chain fatty esters include isostearyl neopentanoate, 2-ethyl-hexyl myristate, isopropyl stearate and isostearyl palmitate. Acceptable tribasic acid esters include triisopropyl trilinoleate and trilauryl citrate. Acceptable straight chain fatty esters include cetyl octanoate lauryl palmitate, myristyl lactate, oleyl erucate

and stearyl oleate. Preferred esters include coco-caprylate/caprate (a blend of coco-caprylate and coco-caprate), propylene glycol myristyl ether acetate, diisopropyl adipate and cetyl octanoate.

Suitable fatty alcohols and acids include those compounds having from 10 to 20 carbon atoms. Especially preferred are such compounds such as cetyl, myristyl, palmitic and stearyl alcohols and acids.

Among the polyols which may serve as emollients are linear and branched chain alkyl polyhydroxyl compounds. For example, propylene glycol, sorbitol and glycerin are preferred. Also useful may be polymeric polyols such as polypropylene glycol and polyethylene glycol.

Exemplary hydrocarbons which may serve as emollients are those having hydrocarbon chains anywhere from 12 to 30 carbon atoms. Specific examples include mineral oil, petroleum jelly, squalene and isoparaffins.

Another category of functional ingredients within the cosmetic compositions of the present invention are thickeners. A thickener will usually be present in amounts anywhere from 0.1 to 20% by weight, preferably from 0.5 to 10% by weight of the composition. Exemplary thickeners are cross-linked polyacrylate materials available under the trademark Carbopol from the B.F. Goodrich Company. Gums may be employed such as xanthan, carrageenan, gelatin, karaya, pectin and locust beans gum. Under certain circumstances, the thickening function may be accomplished by a material also serving as a silicone or emollient. For instance, silicone gums in excess of 10 centistokes and esters such as glycerol stearate have dual functionality.

Various types of active ingredients may be present in cosmetic compositions of the present invention. Actives

are defined as skin benefit agents other than emollients and other than ingredients that merely improve the physical characteristics of the composition. Although not limited to this category, general examples include sunscreens, tanning agents, other skin anti-wrinkling agents, and anti-acne agents.

A preferred optional active ingredient to be included in the inventive composition are ceramides which play an important role in the production and maintenance of the water permeability barrier of the skin. Suitable ceramides and synthetic analogues thereof are disclosed in European Patent Application 534 286, European Patent application 282 816, European Patent Application 227 994, U.S. Patent 5,175,321, U.S. Patent 4,985,547, U.S. Patent 5,028,416, U.S. Patent 5,071,971, Japanese Patent Application 63192703, U.S. Patent 4,468,519, and U.S. Patent 4,950,688, all of which are incorporated by reference herein. Ceramides or their synthetic analogues may be present in the inventive compositions at a level of from 0.00001 to 5%, preferably from 0.0001 to 1%, optimally from 0.01 to 0.5%.

A particularly beneficial combination of lipids (e.g., ceramides or phospholipids) with carboxylic acids and sterols preferably is incorporated in inventive compositions. The combination is disclosed in greater detail in U.S. patent application 08/007,468 incorporated by reference herein.

Sunscreens include those materials commonly employed to block ultraviolet light. Illustrative compounds are the derivatives of PABA, cinnamate and salicylate. For example, octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone (also known as oxybenzone) can be used. Octyl methoxycinnamate and 2-hydroxy-4-methoxy benzophenone are commercially available under the trademarks, Parsol MCX and

Benzophenone-3, respectively. The exact amount of sunscreen employed in the emulsions can vary depending upon the degree of protection desired from the sun's UV radiation.

Vitamins such as vitamins A, E, C, and D and their derivatives may also be included in the compositions of the present invention, especially preferred is vitamin A palmitate (retinyl palmitate) and vitamin E linoleate (tocopheryl linoleate). Other esters of vitamins A and E may also be utilized.

Many cosmetic compositions, especially those containing water, must be protected against the growth of potentially harmufl microorganisms. Preservatives are, therefore, necessary. Suitable preservatives include alkyl esters of p-hydroxybenzoic acid, hydantoin derivatives, propionate salts, and a variety of quaternary ammonium compounds.

Particularly preferred preservatives of this invention are methyl paraben, propyl paraben, imidazolidinyl urea, sodium dehydroxyacetate and benzyl alcohol. Preservatives will usually be employed in amounts ranging from about 0.5% to 2% by weight of the composition.

Other adjunct minor components may also be incorporated into the cosmetic compositions. These ingredients may include colouring agents, opacifiers and perfumes. Amounts of these materials may range anywhere from 0.001 up to 20% by weight of the composition.

The following specific examples further illustrate the invention, but the invention is not limited thereto.

EXAMPLES 1-5

MEASUREMENT METHOD:

Corneocyte Release Assay

The corneocyte release assay was utilized in order to investigate the effect of alpha hydroxy acid (alone or in the presence of various chelators) on skin desquamation. Split thickness cadaver skin was washed for 15 minutes in phosphate-buffered saline to remove any loosely held corneocytes. Thereafter, 4mm punch biopsies were obtained and placed into 1.5ml microfuge tubes (2 biopsies per tube) containing 400μl of the test solution consisting of 0.1M Tris-HCI (pH 7.4 with triethanolamine), a chelator, 0.02% sodium azide and an alpha hydroxy acid. Controls utilized the same solution in the absence of any chelators. Following incubation for 20 hours at 37°C the tubes were vigorously vortexed for 30 seconds and the biopsies were removed. The remaining solution containing the released corneocytes was centrifuged at 11,000xg for 5 minutes to obtain a corneocyte pellet. Released corneocytes were counted using a hemacytometer (Hausser Scientific "Brightline" Hemacytometer).

All samples were an average of three replicates. The results that were obtained are summarized in Table 2.

Table 2

Effect of Chelators on Hydroxy Acid-mediated Corneocyte Release

EXAMPLE #	SAMPLE	% CONTROL	P-VALUE
	300mM 2-OH-Octanoic (Control A)	100	-
1	Control A + 5 mM EDTA	171	0.05*
2	Control A + 5 mM Pyrophosphate	159	0.05*
3	Control A + 5 mM 8-hydroxy quinoline	150	0.06*
4	Control A + 5 mM EGTA	118	0.20**
	5 mM Alpha Hydroxy Lauric Acid (Control B)	100	-
5	Control B + 5 mM EDTA	249	0.08*

* indicates significantly different from control at ($p < 0.1$)

** not significantly different from control ($p > 0.1$)

The chelators (EDTA, pyrophosphate, EGTA and 8-hydroxy quinoline) in the absence of any alpha hydroxy acids did not stimulate any release of corneocytes.

Examples 1-3 and 5 are within the scope of the invention (as shown in Table 1, EDTA, pyrophosphate and 8-hydroxyquinoline satisfy the requirements for Mg and/or Zn

binding affinity). Examples 1-3 and 5 demonstrate synergistic interaction between chelators which have high affinity with Mg^{2+} and/or Z_N^{2+} ions and alpha hydroxy acids.

Example 5 demonstrates a particularly strong synergy between chelators within the scope of the invention and longer chain (e.g., C_{12}) alpha hydroxy acids.

Comparative Example 4, which is not within the scope of the invention, demonstrates that chelators which do not have the affinity with magnesium ion of greater than 1.9 and/or the affinity with zinc ion of greater than 9.2 do not significantly enhance the activity of an alpha hydroxy acid.

Example 6

The following composition for topical application to skin was prepared:

Procetyl AWS®	6.3
Proglyceryl 6 Oleate®	14.7
Labrasol®	17.6
Deionized Water	0.166
L-Lactic Acid (99% solution)	9.524
EDTA	0.2
Schercemol 185®	20.68
Trivent OC-16®	16.28
Silicone Fluid 344®	8.8
Squalene	5.5
Ceramide II	0.25

EXAMPLE 7

The following composition for topical application to skin was prepared:

Sphingolipid E®	2.4
Cholesterol	0.6
Stearic Acid	0.7
Sodium Stearate	0.3
L-Lactic acid 99% solution	5.0
Sodium pyrophosphate	0.3
Glycerol	1.0
Xanthan Gum	0.3
Glydant Plus®	0.2
Water	88.5

Example 8

The following composition for topical application to skin was prepared:

Sphingolipid E®	2.4
Cholesterol	0.6
Stearic Acid	0.7
Sodium Stearate	0.3
L-Lactic acid (99% solution)	5.0
Alpha Hydroxy lauric acid	0.1
Sodium pyrophosphate	0.3
Glycerol	1.0
Xanthan Gum	1.0
Glydant Plus®	0.2
Water	88.4

EXAMPLE 9

Effect of the stereo form of an alpha hydroxy acid on increasing skin flexibility

Increased skin flexibility corresponds to a decrease or absence in skin flakiness and dryness. Skin flexibility is measured in vitro by stratum corneum extensibility test.

In vitro Stratum Corneum Extensibility

To examine the effect of a stereoisomers of alpha hydroxy acid (L or D) on stratum corneum samples were first equilibrated to 44% relative humidity (RH) by suspending the samples over a saturated salt solution of potassium

carbonate. After equilibration they were extended by 2% of their original length at 20mm/min using a linear extensometer. The amount of force required to extend the sample was computed and the information displayed as a force extension graph on a personal computer (Amstrad 1640 HD20). The initial slope of the curve in the Hookean region was then be used as an indicator of the integrity of the stratum corneum (gram-force/100% extension). 50μl of a tested stereoisomer of an alpha hydroxy acid was then applied to the external surface of five pieces of the stratum corneum samples and rubbed in with 20 strokes of a gloved finger. The samples were then equilibrated to 80% RH by suspending over a saturated salt solution of ammonium sulphate in humidity chambers and incubated at this humidity for three hours. The samples were then reequilibrated to 44% RH and after conditioning restretched to 2% extension. Results were then expressed as extensibility ratios of before/after treatment. The same test was run for 4% extension.

The results that were obtained are summarized in Table 3:

TABLE 3

	EXTENSIBILITY RATIO AT 44% RH	
ISOMER (2% solutions)	2% EXTENSION	4% EXTENSION
L - lactic acid	3.29 $\pm$ 1.86	1.84 $\pm$ 0.28*
D - lactic acid	1.89 $\pm$ 0.56	1.32 $\pm$ 0.22

* significantly different from D-lactic acid

The results summarized in Table 3 clearly show the superior performance of L isomers in increasing stratum corneum flexibility.

EXAMPLE 10

Effect of Stereochemical Isomers of Alpha Hydroxy Acid on Inhibiting Keratinocyte Differentiation

Adult human epidermal keratinocytes were grown to confluence on T-25 plastic flasks in keratinocyte Growth Medim (KGM) at 37°C under an atmosphere of 5% CO_2 and 95% air. Thereafter the cells were subcultured 24 well dishes and grown to approximately 85% confluence prior to dosing with KGM containing 1.2 mM calcium chloride to stimulate differentiation and therefore envelope formation. Envelope formation is representative of stratum corneum formation in vitro. The inhibitory effects of D and L alpha hydroxy acids on envelope formation were tested by adding 0.1 mM of each to the calcium supplemented KGM buffer. Media was changed every 2 days and after 13 days the cells were harvested for evaluating the total number of cornified envelopes present in the media and the cultured wells. Control samples did not contain any alpha hydroxy acids in the media.

The increase in keratinocyte differentiation accompanies abnormal conditions of stratum corneum, such as skin disorders and skin dryness.

The results that were obtained are summarized in Table 4:

TABLE 4

SAMPLE	TOTAL ENVELOPES ($x10^4$)	% INHIBITION OF ENVELOPE FORMATION (RELATIVE TO CONTROL)
Control	264	-
L - lactic	173	35*
D - lactic	219	17**

* indicates significantly differs from control @ $p<0.05$; Average of 3 replicates.

** not significantly different from control; average of 3 replicates.

The data in Table 4 indicate that the steroisomers of alpha hydroxy acids impart a dissimilar effect on keratinocyte differentiation as measured by cornified envelope formation: the L-form of alpha hydroxy acid was more potent than the D form in inhibiting the differentiation process and therefore the L-stereoform may be more beneficial in treating hyperkeratotic skin conditions. Additionally, these data indicate that lower levels of L-lactic acid compared to either the racemic or D-form would be required to provide comparable efficacy. As lower levels would be utilized, it is likely that less adverse effects would also be encountered without a loss in clinical effectiveness.

EXAMPLE 11

Effect of Stereochemical Isomers of Alpha Hydroxy Acids on Keratinocyte Proliferation

Keratinocyte proliferation (which is indicative of skin

thickness and skin proliferative capacity) decreases with age. Thus, the increase in keratinocyte proliferation is beneficial to counteract skin aging (i.e., wrinkles, thickness, elasticity, and repair).

Adult human keratinocytes were seeded (pipetted) into 12 well plates at a density of 5 x 10^4 cells per well. 24 hours later, the cells were treated with keratinocyte basal medium containing low calcium (0.15 mM Ca^{2+}) containing 0.2 mM of either D- or L-alpha hydroxy acid. Four wells were dosed per solution. After 48 hours, cells were harvested and counted using a hemacytometer (Hausser Scientific "Brightline" Hemacytometer). Control samples were run in the absence of any alpha hydroxy acids. The results that were obtained are summarized in Table 5.

TABLE 5

	% INCREASE RELATIVE TO CONTROL
L - lactic acid	135*
D - lactic acid	104**

*significantly different from control
**not significantly different from control

The data in Table 5 indicates that the L-form of alpha hydroxy acid is significantly superior to the D-form in eliciting keratinocyte proliferation.

The ingredients included in the Examples may be obtained from the following suppliers:

TRADENAME	INGREDIENT	SUPPLIER
Sphingolipid E®	Sphingolipids	Lancaster
Ceramide II®	Sphingolipids	Quest
Stearic Acid	Stearic Acid	Lancaster
Sodium Stearate	Sodium Stearate	Witco
Cholesterol	Cholesterol	Lancaster
Purac D(-) HS®	D-Lactic Acid	Purac
Purac USP88®	L-Lactic Acid	Purac
Alpha Hydroxy Lauric Acid	Hydroxydodecanoic acid	Sigma
Sodium pyrophosphate	Sodium pyrophosphate	J.T.Baker
Procetyl AWS®	PPG-%-Ceteth-20	Croda
Polyglyceryl 6 Oleate®	Polyglyceryl 6 Oleate	Gattefosse
Labrasol®	PEG-8-Caprylic/Capric Triglyceride	Gattefosse
EDTA	EDTA	Hampshire
Schercemol 185®	Isostearyl Neopentanoate	Scher
Trivent OC-16®	Cetyl Octanoate	Trivent
Silicone Fluid 344®	Cyclomethicone	Dow Corning
Squalene	Squalene	Robeco
Glycerol	Glycerin	Baker
Glydant Plus®	DMDM Hydantoin and Iodopropynyl Butylcarbamate	Lonza
Keltrol 1000®	Xanthan Gum	Kelco

It should be understood that the specific forms of the invention herein illustrated and described are intended to be representative only. Changes, including but not limited to those suggested in this specification, may be made in the illustrated embodiments without departing from the clear teachings of the disclosure. Accordingly, reference should be made to the following appended claims in determining the full scope of the invention.

CLAIMS

1. A composition for topical application to mammalian skin, the composition comprising:

(a) from 0.001% to 70% of a skin benefit ingredient selected from the group consisting of an alpha hydroxy acid, a salt thereof, an ester thereof, and mixtures thereof;

(b) a chelating agent in an effective amount to enhance the activity of the skin benefit ingredient, wherein the chelating agent is selected from the group consisting of chelating agents having an affinity with zinc ion of greater than 9.2, chelating agents having an affinity with magnesium ion of greater than 1.9, and mixtures thereof; and

(c) a pharmaceutically acceptable vehicle in an amount effective to deliver the skin benefit ingredient.

2. A composition according to claim 1 wherein at least 60% of the skin benefit ingredient by weight of total skin benefit ingredient is in L stereoform.

3. A composition according to claim 1 or claim 2 wherein the chelating agent is selected from the group consisting of ethylene diamine tetraacetic acid, a salt of ethylene diamine tetraacetic acid, a salt of diphosphoric acid, a salt of polyphosphoric acid, 8-hydroxyquinoline, DL-(Methylethylene)dinitrolo tetra acetic acid, trans-decahy- dronaphthylene-trans-2,3-bis-iminodiacetic aminophenyl methylene diphosphonic acid, ethylene bis-N,N^1(2,6-dicarboxyl)piperdine, adenosine triphosphate, and mixtures thereof.

4. A composition according to any one of claims 1 to 3 wherein the chelating agent is present in an amount of at least 0.2% by weight of the composition.

5. A composition according to any one of claims 1 to 4 wherein the skin benefit ingredient includes at least 8 carbon atoms.

6. A composition according to any one of claims 1 to 5 wherein the skin benefit ingredient includes at least 10 carbon atoms.

7. A composition according to any one of claims 1 to 6 wherein the skin benefit ingredient comprises lactic acid, alpha hydroxy lauric acid, or alpha hydroxy octanoic acid or a salt thereof, an ester or ester thereof and mixtures thereof.

8. A composition according to any one of claims 1 to 7 wherein the skin benefit ingredient is present in an amount from 0.1% to 20% by weight of the composition.

9. Use of a composition according to any one of claims 1 to 8 in improving or preventing the appearance of wrinkled, flaky, aged or photodamaged skin or in skin disorders.

10. A method of improving or preventing the appearance of wrinkled, flaky, aged, photodamaged skin, or skin disorders, the method comprising applying to the skin the composition of claim 1.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/EP 94/02456

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	EP,A,0 608 433 (SHISEIDO COMPANY LIMITED) 3 August 1994 see page 2 see page 3, line 1 - line 6 see page 3, line 43 - line 53 see page 8, line 16 - line 34 see examples 1-5,1-7,1-8	1,3,4, 7-10
X	WO,A,93 09213 (BLYCOR INTERNATIONAL LTD.) 13 May 1993 see claim 1 4 9.	1,3,4,7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 November 1994	12. 12. 94

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati Application No
PCT/EP 94/02456

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